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A Study of COVID-19 Mortality Under Varying Patient Frailty

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Abstract

For this study, we modeled the spread and mortality of COVID-19 throughout the city of Chicago. By incorporating group frailty into a classic SEIR infectious disease model, we were able to differentiate the population of Chicago by their response to COVID-19. Three age groups with different COVID-19-induced death rates were examined, and the model sought to showcase the multiplicative deviation of each age group death rate from the average disease-induced death rate. This adjustment for different death rates among age groups accounted for heterogeneity within the population, and sought to introduce a more accurate manner for modeling the spread of infectious diseases.

Keywords: ageing, COVID-19, frailty, infectious disease modeling, SEIR

1 Introduction

Infectious disease modeling is used to study, analyze, and interpret the spread of infectious diseases through a population. One common model used for infectious disease spread is the SEIR compartmental model, showcasing movement between four classes: the susceptible, exposed, infectious, and recovered / removed. SEIR models generally assume that all individuals move between classes at the same rate [6, 7]. The focus of this work is to take a closer look at how different subgroups within a population respond to the transitions between the S, E, I, and R states. This focus showcases heterogeneity within a population. One method for incorporating heterogeneity within an SEIR model is to break down the typical classes into subclasses. These subclasses allow for differentiation within a population based on noticeable response to an infectious disease. Regarding factors differentiating subclass response to a disease, one can examine group frailty. Frailty, in a medical sense, marks a difference in response due to varying health factors [16]. From a mathematical standpoint, frailty is a multiplicative effect on the hazard function of a group of individuals [11]. Those individuals considered to be more frail, whether due to internal characteristics or external circumstances, undergo a multiplicative effect on their corresponding death rate. This work incorporates the concept of frailty to develop an SEIR frailty-structured model accounting for heterogeneity within classes, as well as a method for estimating the multiplicative effect distinguishing this frailty-induced heterogeneity. The multiplicative effect due to frailty is defined as the frailty parameter. To demonstrate one method for estimating frailty parameters within a frailty-structured model, we sought to model the spread of the coronavirus COVID-19 throughout the city of Chicago in Illinois. We focused our model on the spread of COVID-19 during the four month period between March 5, 2020 and July 5, 2020, as the city of Chicago collected daily COVID-19 related data during this time period.

Coronaviruses are a subset of viruses causing illness in animals and sometimes humans depending on the development of the virus. In particular, symptoms for the coronavirus COVID-19 may include a consistent cough, fever, shortness of breath, and body aches. Infected individuals may also experience a sore throat, loss of taste and smell, diarrhea, as well as a recurring headache [17]. Some individuals infected with COVID-19 may develop COVID-related pneumonia, causing a phlegm-filled cough in addition to other COVID-19 symptoms [16].In this way, COVID-19 symptoms vary in their seriousness and longevity depending on the individual. Although infected individuals of all ages have undergone serious symptoms and required hospitalizations, older populations are specifically considered at high risk for COVID-19 [2]. This risk is attributed to the relationship of age and comorbidities. Comorbidities describe the accumulation of existing factors / conditions that can impact response to an immediate or primary condition, such as a disease. Some conditions occurring together that can be considered comorbidities include hypertension, high cholesterol, diabetes, dementia, and more [18]. Comorbidities are associated with age as the number of comorbidities accumulated increases as age increases [5]. Individuals over the age of 65 are especially associated with having devel-

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oped more conditions in co-occurrence, thus having developed more comorbidities [5]. These comorbidities lead to complications regarding individual response to diseases such as COVID-19. Since age is associated with development of comorbidities and increased risk factors, age can be considered a factor differentiating a population by response to disease, or by individual frailty.

Alongside comorbidities serving as a link between age and frailty, age has been defined as a frailty itself. A study examining pneumonia risk factors considered age a frailty factor, defining frailty as "a distinct clinical syndrome characterized by a decrease in physiological reserve and resistance to stressful situations, making individuals more vulnerable to health problems" [12]. Another study provides evidence that age increases rates of chronic disease and impairments [3]. Whatsmore, one study formally defined aging as "changes in immune response impairment of alveolar macrophage function and increase in cellular apoptosis during sepsis, leading to a greater severity of infection" [4]. This study went on to suggest that "biological age should be more routinely assessed to guide clinical decision making in older patients in general and, in particular, to help clinicians identify older patients with pneumonia who might benefit from ICU admission." While this study focuses on pneumonia rather than COVID-19, pneumonia is a possible complication of COVID-19, and it is important to note the risk associated with age in non-COVID pneumonia patients. This study determined that age was a frailty affecting mortality of pneumonia patients [4].

As a result of this evidence and available data, throughout this work, we consider frailty in the context of age. This means that as we proceed towards accounting for variation due to "frailty," and build upon the compartmental SEIR infectious disease model, we are really examining the effects of aging on patient response to an infectious disease. While frailty can account for any internal or external attribute impacting individual response to a disease, we focus in on aging as a characteristic marker for frailty. However, we continue to refer to variation in response to disease through the general term "frailty" throughout this work as our model and method may be modified to address variation due to any factor affecting frailty. Yet for our specific case study, the term "frailty" is considered interchangeable with ageing. From a public health standpoint, older individuals are presumed at higher risk for COVID-19, such that they are more likely to undergo worsened symptoms and may require hospitalization [2]. To mathematically estimate just how age affects an individual's frailty for COVID-19 mortality, age group death rates were estimated using data collected from the city of Chicago.

The city of Chicago was among the "hot spots" when the COVID-19 outbreak reached the United States. The terminology "hot spot" refers to a location in which the number of cases arose rapidly. Hot spots also refer to locations containing more cases than most other locations in the country at the time. The city of Chicago, as well as the entirety of the state of Illinois, took immediate response to rising case numbers and concerns regarding COVID-19. As a result of measures put in place to limit the spread of COVID-19 throughout Illinois, the number of in-person interactions among Chicago residents was forcibly lessened for the majority of the outbreak. This consistent and immediate response marked Chicago as an adequate place to model. Moreover, the consistency of the Chicago-central outbreak was considered a good measure for adequately meeting the assumptions of the compartmental SEIR model. The SEIR model assumes homogeneous interaction, spatial homogeneity, and temporal homogeneity [6, 1]. Modeling the entirety of the United States, for example, would break the assumption of homogenous interaction as not everyone in the United States is interacting with an equal number of people each day. Even modeling on a smaller scale, say the entirety of Illinois, breaks the assumption of spatial homogeneity as people living in rural areas theoretically interact with fewer people daily when compared with people living in urban areas. Averaging interaction and infection rates across rural and urban areas may lead to spurious conclusions if left unacknowledged. Chicago, as a centralized and strictly urban location, was considered to be more consistent in its number of daily in-person interactions. In addition, Chicago more closely meets the assumption of spatial homogeneity (as an all urban location) than the state of Illinois or the entirety of the United States. Furthermore, Chicago remained uniform in it's lockdown policy for the majority of the outbreak, only opening up once the number of daily cases lessened. Using the Chicago-central outbreak as a case study, data collection and the method for introducing frailty to different age groups is outlined in the Methods section below.

2 Methods

2.1 Collecting Data

Data containing daily COVID-19 deaths and confirmed cases between March 5, 2020 and July 5, 2020 was collected from the City of Chicago website and published to HealthData. This data contained the number of both COVID-19 cases and deaths for varying demographics within Chicago. More specifically, the dataset included COVID-19 mortality and case counts for eight different age groups: ages younger than 18, ages 18–29, ages 30–39, ages 40–49, ages 50–59, ages 60–69, ages 70–79, and ages 80 and older. As an overview, the total COVID-19 mortality and confirmed case counts for each age group

Table 1: Covid-19 Age-Stratified Confirmed Cases, Number of Deaths

Group	Age	Confirmed Cases	Deaths	Death Rates
1	<18	2,636	2	0.000758725
2	18–29	10,090	18	0.001783944
3	30–39	9,521	65	0.006827014
4	40–49	9,612	142	0.0147732
5	50–59	9,024	289	0.032025709
6	60–69	6,400	573	0.08953125
7	70–79	3,477	652	0.187517975
8	80–89	2,751	893	0.324609233

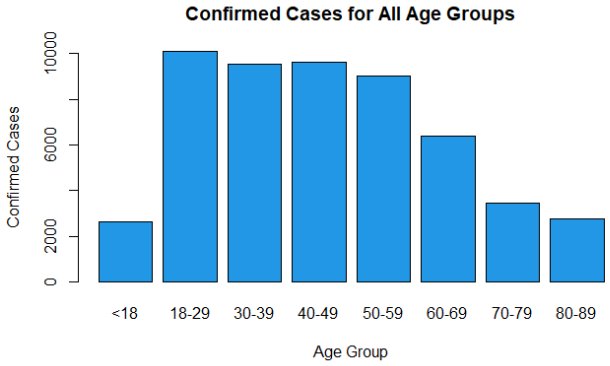


Figure 1: Age group total confirmed cases for COVID-19 as of July 5, 2020.

are included in Table 1.

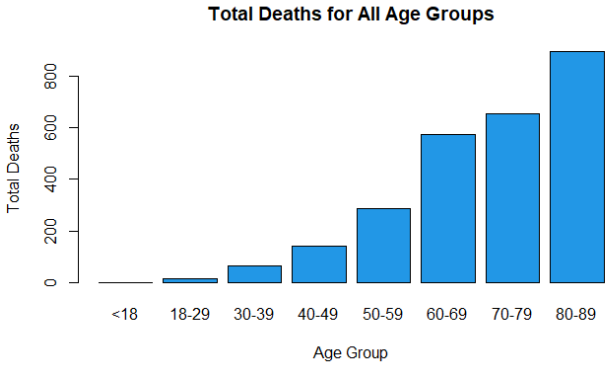


Figure 2: Age group total deaths for COVID-19 as of July 5, 2020.

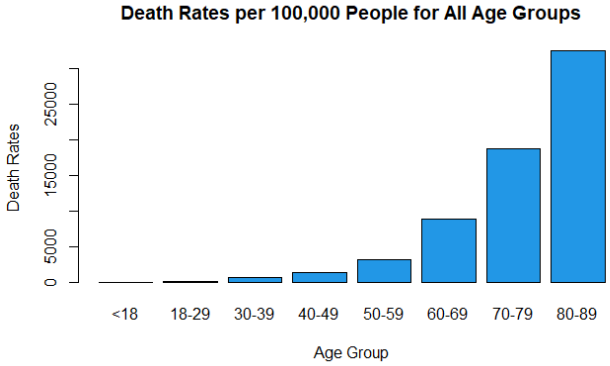


Figure 3: Age group death rates for COVID-19 as of July 5, 2020. Deaths rates are calculated per 100,000 people.

2.2 Data Exploration

2.2.1 Combining Age Group Data for Frailty Estimation

The data in Table 1 provides the total number of COVID-induced deaths and confirmed COVID-19 cases for eight age groups. When investigating differences in frailty, it is not especially important to look at each of these particular age groups separately. Instead, we want to focus on groups displaying obvious differences in the number of deaths per the corresponding number of confirmed cases. Examining a bar graph of the number of confirmed cases per age group, shown in Fig. 1, notice that the majority of COVID-19 cases are among age groups 2–5, corresponding to ages 18–59. Interestingly, despite there being more cases within age groups 2–5, these age groups have fewer total deaths than age groups 6–8. A bar graph for age-stratified total COVID-19 deaths is provided in Fig. 2.

To gain a visual perspective on how the number of deaths within each age group compares to the corresponding number of cases, age group death rates were plotted in Fig. 3.

The overall shape of the bar graph for age group death rates is similar to the overall shape of the bar graph for age group deaths. The shape of the bar graph for age group confirmed cases, however, is not similar to that of the graph for deaths and death rates.

This indicates that the proportion of deaths to the number of cases is not the same for each age group. These proportional differences reflect the difference in response to COVID-19, such that not all age groups respond the same. Since age groups 6–8 maintained high death rates while age groups 2–5 had lower death rates, these clusters of age groups were each grouped together into two separate groups. Furthermore, the youngest age group within the dataset was included as a separate third group. This grouping was completed to showcase noticeable variation in response to COVID-19. If the original eight age groups collected from the city of Chicago dataset were each utilized for comparison, we would expect that some

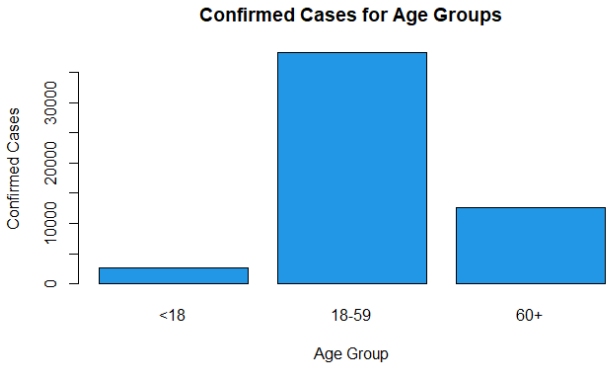
age groups, such as age groups 2–5, would have similar estimates for frailty. Therefore, we would expect those similar age groups to have similar estimations for the number of cumulative deaths. To avoid having excess similar groups, and to focus on variation as a result of age, the data was reorganized to display three age groups rather than eight. These three age groups were chosen in correspondence with CDC guidelines regarding the impact of age on COVID-19 response. It is common in frailty modeling to build models based on descriptive characteristics, such that when frailty parameters are involved, empirical determinations are commonly used. The three age groups in accordance with CDC guidelines contained individuals less than 18 years old, individuals between 18–59 years old, and individuals 60 years old and older. Bar graphs for total confirmed cases, total deaths, and death rates for the organized three age groups are outlined in Fig. 4.

These three groups exemplify the difference in COVID-19 death rates among age groups. The death rate for the eldest age group (ages 60 years and older) appears much higher from a visual standpoint. To examine just how much more at risk older groups are, we used the data for all three age groups to estimate the frailty for each group. The frailty for each group indicates the multiplicative deviation from the average death rate, thereby showcasing the higher or lower mortality rates experienced by different age groups.

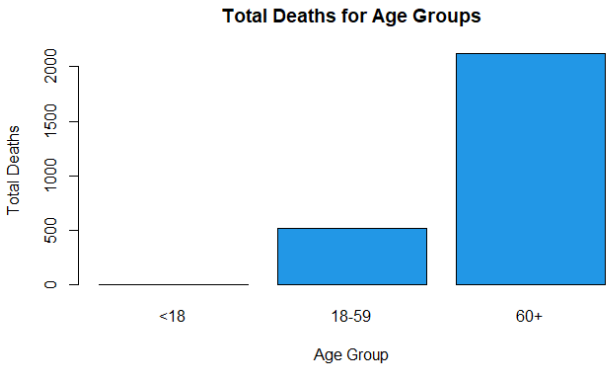
2.3 Estimating Frailty Using Age Grouped Data

Frailty is a multiplicative effect on the death rate that differentiates a population by some characteristic putting some individuals at an advantage and others at a disadvantage. Frailty parameters are indices indicating the frailty of different groups. They serve as weights that either inflate or deflate the main parameter of a model, showcasing the contribution of a given factor on another factor. For instance, values less than 1 indicate a decreased frailty and values greater than 1 indicate an increased frailty. It is important to note that frailty parameters can be any positive real number estimating the multiplicative deviation of differentiated group death rates from the overall average death rate. The average death rate stems from the total number of deaths out of the size of the population at risk (in our case Chicago). Therefore, when calculating the frailty parameter, we find the multiplicative deviation of each group death rate from the overall death rate. In this way, the frailty parameter is calculated by dividing the age group specific death rate by the age-stratified death rate.

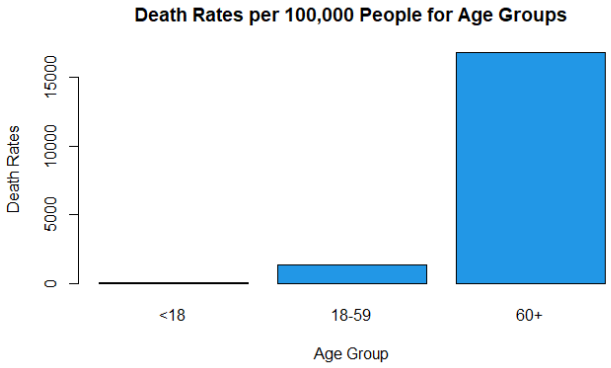
We find the average death rate by first calculating the number of deaths divided by the size of the population. According to 2020 estimates, the estimated population



(a) Age group total confirmed cases as of July 5, 2020.



(b) Age group total deaths as of July 5, 2020.



(c) Age group death rates for COVID-19 as of July 5, 2020. Deaths rates are calculated per 100,000 people.

Figure 4: Age group COVID-19 confirmed cases, deaths, and death rates as of July 5, 2020.

Table 2: Total Deaths and Cases for Age Group Data

Group	Age	Deaths	Population Size	Deaths Per Pop.
1	<18	2	576,625	0.000003
2	18–59	514	1,676,504	0.000307
3	60+	2,118	465,426	0.004551
All	All	2,634	2,718,555	0.000969

Table 3: Frailty Parameter Estimation

Group	Age	Death Rate	Average Death Rate	Frailty Parameter
1	<18	0.000003	0.000969	0.003580
2	18–59	0.000307	0.000969	0.316432
3	60+	0.004551	0.000969	4.696752

size of Chicago was 2,718,555. Thereby, the average death rate is 2,634 divided by 2,718,555. This gives an average death rate of 0.000969, or 96.89 deaths per 100,000 people. If there was no frailty, this death rate is the average expected death rate per each age group. However, since some age groups are advantageous in their response to COVID-19 while others are at a disadvantage, this weighted average death rate is not the reality for each age group. Frailty parameters are then used to indicate each age group's deviation from the average death rate.

These parameters are estimated by finding the multiplicative deviation of each age-specific death rate from the weighted average death rate. These three frailty parameter estimates—0.00357980, 0.316432351, and 4.696752426—are the multiplicative factors showcasing each age group's deviation from the average death rate. Using each frailty parameter, the goal was to more accurately reflect age-stratified mortality for COVID-19 and build a mathematical method of frailty into the classic SEIR infectious disease model. This method sought to tie together medical knowledge of frailty with disease spread. To investigate the adequacy of including these frailty parameters, we built an SEIR model with incorporated frailty.

3 Model

3.1 Developing a Frailty-structured SEIR Model

3.1.1 The Basics

To develop a frailty-structured SEIR model, the typical SEIR model was first examined as a base for building upon. This basic preliminary SEIR model is included below.

$$\frac{dS}{dt} = -\beta S(I/N) \tag{1.1}$$

$$\frac{dE}{dt} = \beta S(I/N) - \zeta E \tag{1.2}$$

$$\frac{dI}{dt} = \zeta E - \gamma I - \delta I \tag{1.3}$$

$$\frac{dR}{dt} = \gamma I \tag{1.4}$$

In Eqs. (1), β is the rate at which susceptibles and the infectious interact and at which the disease is spread, ζ is the rate at which the exposed move into the infectious class, γ is the rate at which the infectious move into the recovered class, and δ is the disease-induced death rate. The parameter N is also included to represent the total size of the population being examined. Thereby, N is the sum of each class, or $N = S + E + I + R$. We divide the infectious class by N for Eq (1.1) to showcase the proportion of infectious people within the population interacting with the susceptible. The parameters β and δ are calculated based on population dynamics and collected data, whereas the parameters ζ and γ stem from medical knowledge regarding the disease. More specifically, ζ is the reciprocal of the average latent period of a disease, and γ is the reciprocal of the average infectious period of a disease multiplied by the percent of recoveries [9, 10]. It is important to note that the flow rates between the susceptible and infectious classes are based on horizontal incidence (where β represents the interaction between the susceptible and infectious) [9, 10]. Furthermore, the flow rates between the exposed to infectious class and the infectious to recovered class are based on the transfer rate of individuals between classes [9]. This means that ζ and γ are the rates at which people move out of the class. Note that this base model does not include a birth rate or natural death rate so that the total population size is assumed to be constant. While Eqs. (1) demonstrates the flow of individuals between classes, the goal was to create a frailty-structured model such that at least one class contains subclasses serving to introduce controlled heterogeneity into the model. As a result, the base model was built upon by creating subclasses for each of the age groups within Table 1.

3.1.2 Introducing Subclasses

There are three age groups in Table 1: ages less than 18, between 18–59, and greater than 60. Since frailty is an effect on the disease-induced mortality rate for different age groups, subclasses were constructed within the infectious and recovered classes of the SEIR model. The assumption here is that everyone is equally susceptible to contracting COVID-19, and since the rate at which exposed individuals move into the infectious class is based

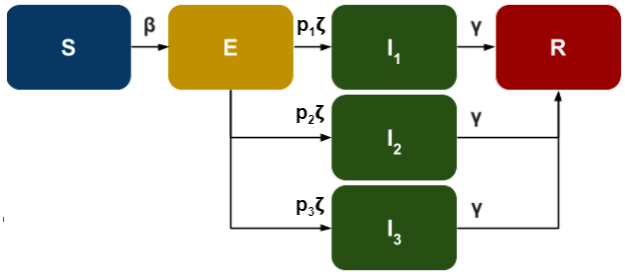


Figure 5: SEIR model with subclasses subdividing the infectious class.

on the latent period of the disease, it is additionally assumed that the rate ζ is the same for all age groups. In terms of frailty, some individuals may be at an advantage and others at a disadvantage once they've contracted COVID-19 and their body is battling symptoms. Therefore the difference in frailty is incorporated into the infectious class where individuals either recover or die as they are battling the disease. As a result, these differences in disease response are showcased by creating subclasses within the infectious class of the SEIR model and altering the disease-induced death rate. These subclasses are visually depicted in Fig. 5.

Each of the infectious subclasses, labeled as I_1, I_2, and I_3, mark a differentiation in the population. The frailty will be introduced regarding each infectious class's COVID-19-induced death rate. For now, this intermediate model with subclasses is represented using the system of differential equations in Eqs. (2).

$$\frac{dS}{dt} = -\beta S(I_1 + I_2 + I_3)/N \tag{2.1}$$
$$\frac{dE}{dt} = \beta S(I_1 + I_2 + I_3)/N - \zeta E \tag{2.2}$$
$$\frac{dI_1}{dt} = p_1\zeta E - \gamma I_1 - \delta I_1 \tag{2.3}$$
$$\frac{dI_2}{dt} = p_2\zeta E - \gamma I_2 - \delta I_2 \tag{2.4}$$
$$\frac{dI_3}{dt} = p_3\zeta E - \gamma I_3 - \delta I_3 \tag{2.5}$$
$$\frac{dR}{dt} = \gamma I_1 + \gamma I_2 + \gamma I_3 \tag{2.6}$$

Proportions of the population in the form of p_1, p_2, and p_3 were included in each infectious subclass equation to reflect the number of people in each age group. These proportions were collected by dividing the number of people per age group by the total number of people within the population. If these proportions had not been included, then the model would assume that all Exposed move into I_1, I_2, and I_3. Instead, we need for those exposed to move only into one of those three classes, so the proportions dependent on age group are used to ensure not all exposed move into each infectious subclass.

3.1.3 Introducing Frailty

While Eqs. (2) creates three subclasses within the Infectious class, it does not differentiate mortality rates between the three classes. To differentiate mortality rates and account for differences in response to COVID-19, the frailty parameters were introduced. These parameters are labeled as ϕ_1, ϕ_2, and ϕ_3, such that they correspond to each age group. Since frailty is a multiplicative effect on the death rate, the overall COVID-19 death rate δ was left in the model, and each of the frailty parameters ϕ_i, where i = 1, 2, 3, were introduced as multiplicative factors on δ. This was intended to showcase the average death rate and the deviation of each age group from this average as a result of differing frailties. The final model with frailty parameters ϕ_i is shown in Eqs. (3).

The model in Eqs. (3) includes the frailty parameters ϕ_i as well as parameters for the natural introduction and removal of individuals to and from the total population. The parameter λ represents the population birth rate and the parameter μ represents the non-COVID-death rate. [1] The parameters λ and μ enable for the size of the total population to grow and diminish from natural causes, such that the disease-induced death rate is not the only way in which people leave the population. These parameters for introducing and removing people to and from a population are important if an outbreak is long-lasting and natural births and deaths would greatly effect the results. If an outbreak occurs more quickly, it is not always necessary for these parameters to be estimated. We leave these parameters as a part of the finalized model so that the model itself can be flexible for different outbreak lengths. While natural birth and death occurrences are considered within the model, the model does not allow for immigration and emigration. Additionally, equations D_1, D_2, D_3 were included to examine the cumulative number of disease-induced deaths per each age group. These equations are focused on the number of COVID-19 induced deaths within their corresponding infectious subclass. This was the final model constructed to be used for analysis.

$$\frac{dS}{dt} = \lambda - \beta S(I_1 + I_2 + I_3)/N - \mu S \tag{3.1}$$
$$\frac{dE}{dt} = \beta S(I_1 + I_2 + I_3)/N - (\zeta_1 + \mu)E \tag{3.2}$$
$$\frac{dI_1}{dt} = p_1\zeta E - (\gamma + \mu + \phi_1\delta)I_1 \tag{3.3}$$
$$\frac{dI_2}{dt} = p_2\zeta E - (\gamma + \mu + \phi_2\delta)I_2 \tag{3.4}$$
$$\frac{dI_3}{dt} = p_3\zeta E - (\gamma + \mu + \phi_3\delta)I_3 \tag{3.5}$$
$$\frac{dR}{dt} = \gamma I_1 + \gamma I_2 + \gamma I_3 - \mu R \tag{3.6}$$

$$\frac{dD_1}{dt} = \phi_1 \delta I_1 \tag{3.7}$$
$$\frac{dD_2}{dt} = \phi_2 \delta I_2 \tag{3.8}$$
$$\frac{dD_3}{dt} = \phi_3 \delta I_3 \tag{3.9}$$

4 Results

To examine how adequately this model reflects the number of deaths within each age group, the software program R was utilized. Initial conditions for each class size were originally input as whole numbers of the entire city of Chicago population. These class sizes were then scaled to be proportions of the entire population for simpler interpretation. Note that $N = S + E + I_1 + I_2 + I_3 + R + D_1 + D_2 + D_3$, where N is the total size of the population. For studying the spread of COVID-19 in Chicago, the total population is the estimated Chicago population size of 2,718,555 people. Using this total population size, initial conditions were set as outlined in Table 4.

Parameter estimations were calculated using the data collected from the City of Chicago, as well as medical knowledge regarding how COVID-19 spreads. Please note that the average COVID-19-induced death rate was more recently estimated at about 0.5 percent [14]. This estimate was used to calculate the disease-induced death rate. The resulting parameter estimations are depicted in Table 5.

Using these parameter estimations, the model was run using the language R for a total of 1,500 time steps, where each time step is set as one tenth of a day. A series of graphs were output within R for referencing the change in size of each class over time. A plot of the total confirmed COVID-19 cases was included for comparison.

Fig. 7 showcases the infectious subclasses. According to Fig. 7, Age Group 2 (the green line) has the highest peak. The larger peak for Age Group 2 can be explained by the actual size of the age group, as Age Group 2 contains everyone between the ages of 18–59. Age Group 1 (the red line) and Age Group 3 (the blue line) both have peaks much lower. Notice that the size of the infectious class is greater for Age Group 1 than for Age Group 3. This graph shows that the eldest age group does not have as many cases as the other age groups. This variation between age groups is consistent with the data for Confirmed COVID-19 cases. For the actual collected data, there are more cases occurring with Age Group 2 than any other age group. Furthermore, there are more cases for Age Group 1 than for Age Group 3. It is interesting to note that the eldest age group has fewer cases yet contains the highest number of COVID-19 deaths. Comparison of COVID-19 mortality data with the model output is illustrated in Figs. 8–10.

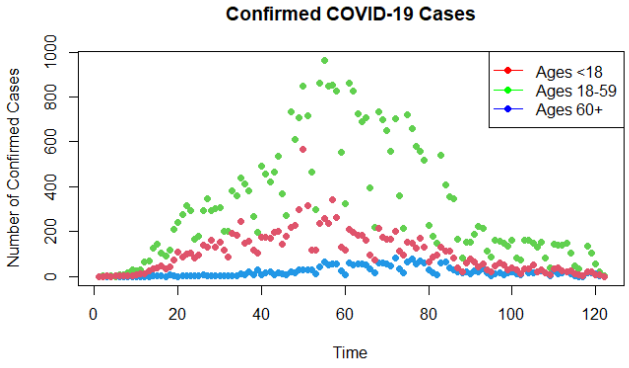


Figure 6: Number of daily COVID-19 confirmed cases for each age group.

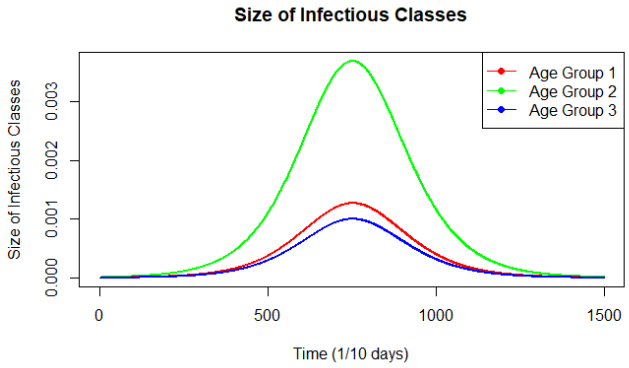


Figure 7: Size of the infectious class for each age group. The size of the infectious class is depicted as a proportion of the entire Chicago population. Age Group 1, Age Group 2, and Age Group 3 refer to Infectious Class 1, Infectious Class 2, and Infectious Class 3 respectively.

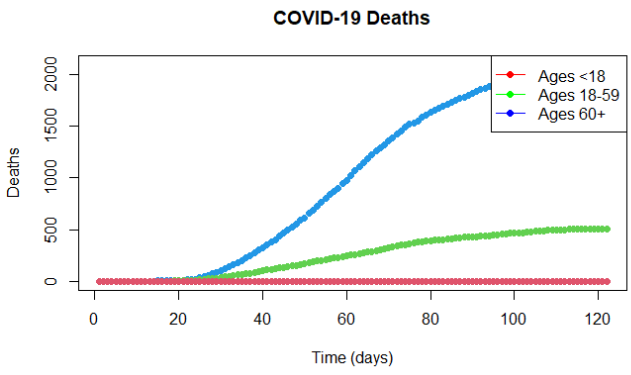


Figure 8: Number of daily COVID-19-induced deaths for each age group.

Table 4: Initial Conditions

Class	Initial Values	Proportion
S	2,718,555	1
E	40	40/2,718,555
I_1	10	10/2,718,555
I_2	10	10/2,718,555
I_3	10	10/2,718,555
R	0	0
D_1	0	0
D_2	0	0
D_3	0	0

Table 5: Parameter Estimations

Parameter	Description	Estimate	Source
λ	Natural birth rate	0.0	Set to zero
β	Interaction rate	0.115	Estimated
μ	Natural death rate	0.0	Set to zero
ζ	Exposed to infectious	0.2	[2]
p_1	Proportion of Age 1	0.212	[13]
p_2	Proportion of Age 2	0.617	[13]
p_3	Proportion of Age 3	0.171	[13]
γ	Recovery rate	$0.1 * 0.995$	[14]
δ	Covid-induced death rate	$0.1 * 0.005$	[14]
ϕ_1	Group 1 frailty	0.003580	See Table 3
ϕ_2	Group 2 frailty	0.316432	See Table 3
ϕ_3	Group 3 frailty	4.696752	See Table 3

The focus of this work was to incorporate the concept of frailty within an infectious disease model, where frailty affects death rate. Since the focus is to examine how accurately our method of frailty models the number of COVID-19 deaths per age group, we compare the mortality data collected with the model output for deaths more closely. The plots for the number of daily COVID-19 deaths and the number of cumulative deaths predicted by the model are illustrated in Fig. 8 and Fig. 10.

If frailty was not included within the model, the cumulative number of deaths for each age group is proportional to the number of cases within each age group, as illustrated in Fig. 9.

When frailty is accounted for, the cumulative number of deaths for each age group more closely reflects the actual data collected, as shown in Fig. 10.

Using the frailty-inclusive model, the number of deaths predicted within Age Group 3 is higher than the number of deaths predicted in both Age Group 1 and Age Group 2 combined. This difference in predicted number of deaths between age groups is consistent with COVID-19 mortality data, where Age Group 3 has a couple thousand COVID-19-induced deaths, while Age Group 1 has at most two deaths and Age Group 2 has fewer than Age Group 3 but more than Age Group 1.

The size of the D1, D2, and D3 subclasses changes over time in that each subclass increases most rapidly during the peak of the size of their corresponding infectious subclasses. The subclass D1 however, has very few deaths occur so this peak is difficult to examine visually. The subclass D2 grows at a faster rate than D1 but at a slower rate that D2. In this way, Age Group 2 does not reach a large cumulative number of COVID-19-induced deaths. Subclass D3 however, increases in size most rapidly at the start of the outbreak and throughout the peak. This rapid increase in the number of COVID-19-induced deaths within Age Group 3 is captured by the

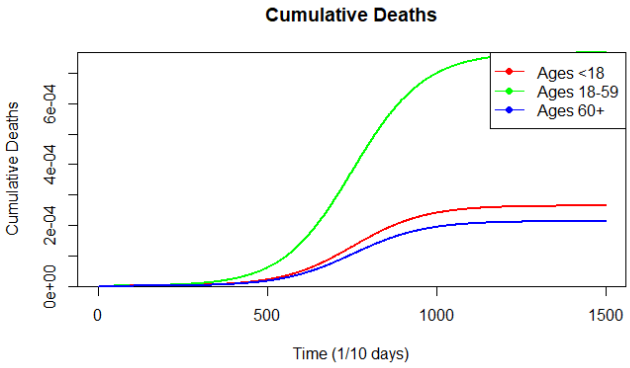


Figure 9: Cumulative COVID-19-induced deaths for each age group when no frailty parameters are included. Cumulative deaths are depicted as proportions of the entire Chicago population.

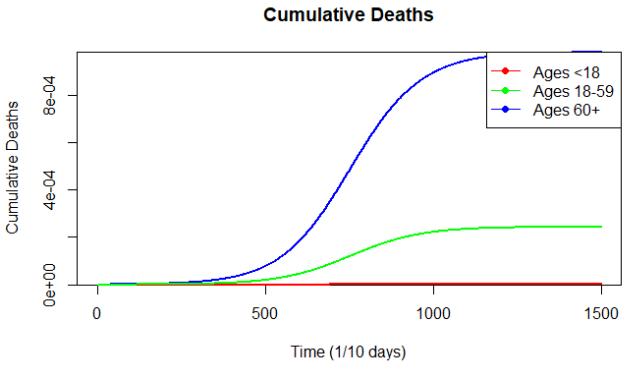


Figure 10: Cumulative COVID-19-induced deaths for each age group when frailty is accounted for. Cumulative deaths are depicted as proportions of the entire Chicago population.

Table 6: Percent Error for the Number of Deaths

Age Group	Actual Deaths	Model Deaths	Absolute Error	Percent Error
0–17	2	2.34	0.34	16.76
18–59	514	599.17	85.17	16.57
60+	2,118	2,416.48	298.48	14.09

frailty parameter ϕ_3 indicating a much larger death rate for the eldest age group. Therefore, Age Group 3 maintains the highest count for cumulative COVID-19-induced deaths. To compare the cumulative predicted number of COVID-19-induced deaths over the course of the outbreak with the current available data, we examine the percentage of error. The percentage of error gives a comparison of how closely the model's cumulative data reflects the actual number of deaths. For the actual number of deaths predicted over time, as well as the calculation for the percentage of error, see Table 6.

Overall, the model predicts a greater number of deaths than the current data contains.This overestimation is attributed to the fact that the model predicts the total number of deaths over the entirety of the outbreak, and the outbreak in Chicago is still ongoing. Therefore, the model is forecasting age-specific deaths past the current data. Please note that Chicago appears to be nearing the end of the first outbreak and is experiencing fewer deaths each day.

5 Concluding Remarks

In conclusion, this work focuses on the concept of frailty and how variation in response to an infectious disease can impact typical infectious disease models. Frailty is incorporated as a multiplicative deviation differentiating age group death rates from the average disease-induced death rate. In this way, frailty is used to showcase how many more times an age-specific death rate differed from the overall average death rate. The 2020 COVID-19 outbreak in Chicago, Illinois is used as a case study to examine how well incorporated frailty parameters model mortality. While the model reflects the data well, the model does follow the assumption that contacts between individuals within a population were consistent from the very beginning to the very end of the outbreak. In actuality, these contact rates changed over time as the city of Chicago first implemented a lockdown and later began to slowly lift social distancing guidelines. These changes in guidelines are important to consider as the number of contacts affects the average expected number of new cases to arise from one singular case, known as the basic reproduction number. Within the model, the basic reproduction number is held constant, whereas realistically this number has changed over time. In this way, the model falls short by taking an averaged basic reproduction number and attributing it to the entire outbreak. Furthermore, our model is based on current data as the outbreak continues to take shape.

Data is continually being collected and as this data changes, our model theoretically would need to be adjusted to better reflect updated parameter estimations. As a result of data limitations, our model is dependent on the available data. Our model is also dependent on medical knowledge regarding the disease of interest—COVID-19. New research is continually being conducted to better understand COVID-19 and the parameters depend on the current understanding of how COVID-19 spreads. Two important parameter estimations stem from the length of the incubation period and infectious period for COVID-19. It is currently unknown whether these periods differ among age groups. As a result, it was assumed for the model that these periods were uniform across age groups. If these periods actually differ as a result of age, the model would further need to be updated. All in all, our parameter estimates and our frailty calculations are dependent on the development of our medical knowledge of COVID-19 and ongoing data collection.

Future work may include the role of policy responses to frailty. This would include changes in quarantine or isolation efforts as a result of estimates of frailty between groups. These changes would provide a feedback loop in the system, and may describe a differential response in behavioral change in the infectious classes. In this case, the general transmission parameter will be replaced by an infectious-subclass-specific transmission rate. That is, the greater the mortality rate of a group, the lower the transmission rate in that group. This would happen after some time in the outbreak, in which the transmission rate would then become a piecewise function and eventually vary the frailty parameters of each group.

Author Contributions

O. Akman and D. Hrozencik conceived of the presented idea. A. Sifuentes investigated the theory and developed the models. All three collaborated, developed, and verified the statistical methods and models equally.

References

[1] Brauer, F. and Castillo-Chavez, C. (2012). Mathematical Models in Populations Biology and Epidemiology. *Texts in Applied Mathematics*, 40:345–409. doi: 10.1007/978-1-4614-1686-9

[2] Centers for Disease Control and Prevention (2019). People Who Are at Increased Risk for Severe Illness. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html

[3] Clegg, A., Young, J., Iliffe, S., Rikkert, M. O., and Rockwood, K. (2013). Frailty in elderly people. *Lancet* (London, England), 381(9868):752–762. doi: 10.1016/S0140-6736(12)62167-9

[4] De Gaudio, A. R., Rinaldi, S., Chelazzi, C, Borracci, T. (2009). Pathophysiology of sepsis in the elderly: clinical impact and therapeutic considerations. *Curr Drug Targets.*, 10(1):60–70. doi: 10.2174/138945009787122879

[5] Divo, M. J., Martinez, C. H., and Mannino, D. M. (2014). Ageing and the epidemiology of multimorbidity. *The European respiratory journal*, 44(4):1055–1068. doi: 10.1183/09031936.00059814

[6] Getz, W. M., Salter, R., and Mgbara, W. (2019). Adequacy of SEIR models when epidemics have spatial structure: Ebola in Sierra Leone. *Phil. Trans. R. Soc. B*, 374:20180282. doi: 10.1098/rstb.2018.0282

[7] Getz, W. M., Salter, R., Muellerklein, O., Yoon, H. S., and Tallam, K. (2018). Modeling epidemics: A primer and Numerus Model Builder implementation. *Epidemics*, 25:9–19. doi: 10.1016/j.epidem.2018.06.001

[8] Guan W-j, Liang W-h, Zhao Y, et al. (2020). Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir* J 2020; 55:2000547 doi: 10.1183/13993003.00547-2020

[9] Hethcote, H. W. (2000). The mathematics of infectious diseases. SIAM Rev. 42, 599–653. doi: 10.1137/S0036144500371907

[10] Keeling M. J. (1999). The effects of local spatial structure on epidemiological invasions. Proceedings. Biological sciences, 266(1421), 859–867. doi: 10.1098/rspb.1999.0716

[11] Klein, J. (1992). Semiparametric Estimation of Random Effects Using the Cox Model Based on the EM Algorithm. *Biometrics*, 48(3):795-806. doi: 10.2307/2532345

[12] Lang, P. O., Michel, J. P., and Zekry, D. (2009). Frailty syndrome: a transitional state in a dynamic process. *Gerontology*, 55(5):539–549. doi: 10.1159/000211949

[13] Levy, J. (2020, June 25th). COVID-19 Daily Cases and Deaths. *City of Chicago.* https://healthdata.gov/dataset/covid-19-daily-cases-and-deaths

[14] Mallapaty, S. (2020, June 16th). How deadly is the coronavirus? Scientists are close to an answer. *Nature.* https://www.nature.com/articles/d41586-020-01738-2

[15] National Foundation for Infectious Diseases (2020, June 26). Coronaviruses. Retrieved from www.nfid.org/infectious-diseases/coronaviruses/

[16] Ruiz, L. A., España, P. P., Gómez, A., Bilbao, A., Jaca, C., Arámburu, A., Capelastegui, A., Restrepo, M. I., and Zalacain, R. (2017). Age-related differences in management and outcomes in hospitalized healthy and well-functioning bacteremic pneumococcal pneumonia patients: a cohort study. *BMC geriatrics,* 17(1):130. doi: 10.1186/s12877-017-0518-0

[17] Sauer, L. M. (2020, July 9th). What Is Coronavirus? *Johns Hopkins Medicine.* Retrieved from www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus

[18] Valderas, J. M., Starfield, B., Sibbald, B., Salisbury, C., and Roland, M. (2009, July). Defining Comorbidity: Implications for Understanding Health and Health Services. *National Institute of Health.* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2713155/